nutritional status of the host population (Ref. 13).

Until the results of additional clincial studies can be better correlated with the IU/mL content of the products containing these toxoids, FDA will retain the current potency tests for the release of each lot of products containing diphtheria toxoid or tetanus toxoid.

15. The Panel recommended that the agency require potency testing after combination of the individual toxoid components in Diphtheria and Tetanus Toxoids (DT) for pediatric use.

FDA agrees with the recommendation. This procedure is followed by all manufacturers and FDA on products submitted to the agency for release.

16. The Panel recommended that regulations concerning the maximum pertussis vaccine dose should be updated to reflect current recommendations and practices. The Panel recommended that pertussis vaccine should have a potency of 4 protective units per single human dose and that the upper estimate of a single human dose should not exceed 8 protective units. The Panel also recommended that the total immunizing dose should be defined as 4 doses of 4 units each compared to the 3 doses of 4 units each now defined in the biologics regulations.

FDA agrees with part of the Panel's recommendations. Currently, ACIP and the Committee on Infectious Diseases of the American Academy of Pediatrics recommended as an immunization schedule for pertussis vaccine a primary series of three doses given at 4- to 8-week intervals, a fourth "reinforcing" dose given 1 year later, and a booster dose administered when the child enters school. FDA agrees that with available vaccines the first four doses are necessary for primary immunization and therefore may be considered as the "total immunizing dose." At the time the additional standards for Pertussis Vaccine were codified (21 CFR 620 Subpart A), the first three doses were defined as the "total immunizing dose" and the potency requirements prescribed in §§ 610.21 and 620.4(g) were set accordingly. FDA did not intend, however, to prescribe in the regulations a specific immunization schedule for administration of the vaccine. Manufacturers of pertussis vaccines are responsible for recommending in their labeling an immunization schedule consistent with the recommendations of ACIP and the Committee on Infectious Diseases. FDA intends to revise and update the additional standards for Pertussis Vaccine. One objective of this revision would be to prescribe potency standards on the basis of a single human dose, rather than the total immunizing dose, thereby removing the existing difference in terminology.

Section 620.4(g) requires that the potency be 12 units per total immunizing dose (3 doses with an estimate of 4 units each) with a minimum acceptable potency of 8 units (or 3 doses of approximately 2.7 units each) and a maximum acceptable potency of 36 units (3 doses of 12 units each). FDA agrees with the objective of establishing 4 units as the minimum potency per single dose and invites submission of further information and comments on this question. All pertussis vaccines tested and released by FDA now meet or exceed the recommended minimum potency, and there is no indication that the vaccines being marketed are not effective.

FDA is unaware of existing data to support a reduction in the upper estimate of potency from 12 to 8 units per single human dose. Unitl such supporting information is provided, FDA disagrees with the Panel's recommendation that maximum potency should not exceed 8 units per single dose.

17. The Panel recommended that the weight-gain test in mice used to determine toxicity of pertussis vaccines be revised to include a reference standard and specifications regarding mouse strain(s) to be used. The Panel also recommended that studies be undertaken to develop assays other than the mouse weight-gain test to predict human reactivity.

FDA does not believe that the use of a standardized mouse strain should be required by regulation. The agency believes that the weight-gain freedom from toxicity mouse test as provided in § 620.5 (21 CFR 620.5) continues to be adequate for ensuring that overtly toxic vaccines are not marketed. There are currently no specifications regarding the mouse strains used for pertussis vaccine testing. A standardized mouse strain, the HSFS/N mouse, has been developed by the Office of Biologics Research and Review, for use in bioassays in general and pertussis vaccine assays in particular. The standardized strain is available for distribution. Every lot of vaccine containing a pertussis component must pass both the manufacturer's and the agency's toxicity and potency assays. FDA believes that confirmatory testing in agency laboratories is an effective method for controlling the variable in pertussis vaccine toxicity assays.

FDA believes that elucidation of the immunochemistry of *Bordetella pertussis* and the development of sensitive and specific tests for protective and reactogenic components of pertussis vaccine are the most productive approaches to provide safe and effective vaccines. Recent studies have defined two potential vaccine components and proposed several other candidate antigens for inclusion in new acellular pertussis vaccines. Pharmacologic, immunologic, and chemical tests, as well as animal tests, are being developed to identify and quantitate these immunogens.

18. The Panel recommended that the agglutination test used to determine pertussis vaccine response in humans should be standardized and that a reference serum should be used for comparison. Also, a reference laboratory should be available at FDA.

FDA agrees with the recommendations. The agency advises that the agglutination test to determine vaccine response in humans has been developed, standardized, and published by agency scientists (Ref. 14). A reference serum and diagnostic antigen are available and a reference laboratory has been established in the Division of Bacterial Products, Office of Biologics Research and Review. In addition, sensitive and specific enzyme-linked immunosobrent assays (ELISA) have been developed to measure *B. pertussis* antigens and quantitate total and individual immunoglobulin responses to human and animal sera and colostrum. The ELISA equipment is automated, has been computer-linked, and is capable of processing large numbers of specimens.

19. The Panel recommended that the pertussis vaccine label should warn that if shock, encephalopathic symptoms, convulsions, or thrombocytopenia follow a vaccine injection, no additional injections with pertussis antigens should be given. The Panel also requested that the label include a cautionary statement about fever, excessive screaming, and somnolence.

FDA agrees with the recommendation, except that the agency believes it is more appropriate to include the information above in the package insert (labeling) rather than on the container or package label.

The recommendations of ACIP (1981) and the Committee on Innfectious Diseases (1982) (Refs. 8 and 15) state that collapse or shock, persistent crying or screaming episodes, temperatures of 40.5 °C or more, and/or convulsions with or without fever following the administration of pertussis vaccine are contraindications to further injections with vaccines that contain a pertussis vaccine component. An evolving

neurologic disorder is a contraindication to the use of pertussis vaccine. In addition, current ACIP recommendations state that severe alterations in consciousness, generalized or focal neurologic signs, system allergic reactions, thrombocytopenia, and hemolytic anemia are contraindications to the continued use of pertussis vaccine. Labeling for products containing a pertussis vaccine component is being revised in accordance with these recommendations.

20. The Panel recommended that any fractionated pertussis vaccine which differs from the original whole cell vaccine should be field tested until better laboratory methods for evaluating immunogenicity are developed; field testing should include agglutination testing and, if possible, evaluation of clinical effectiveness.

FDA agrees with the recommendation. No vaccine containing a fractionated pertussis component is currently being manufactured under license in the United States; however, FDA agrees with the Panel that clinical trials of candidate fractionated pertussis vaccines should provide evidence that disease is prevented as proof of efficacy until better laboratory methods are developed for evaluating immunogenicity in humans. The propriety of agglutination testing will be considered on an ad hoc basis.

Research to develop a new generation of acellular pertussis vaccines is in a dynamic state; thus, it is difficult to predict what tests would be necessary to demonstrate the effectiveness of a newly developed acellular pertussis vaccine. The problems associated with the clinical evaluation of such vaccines were discussed at a workshop, "New Pertussis Vaccines—Laboratory and Clinical Evaluation", sponsored by FDA's former Bureau of Biologics, NIAID, and CDC on February 11 and 12, 1982.

21. The Panel recommended that adequate public support be provided for studies of the pathogenesis of pertussis and the biology of the organism, particularly as related to the immunology of pertussis, the complications of the disease, and the untoward reactions to immunization.

FDA agrees with the recommendations. Support should be provided for both the extramural and intramural basic research necessary to develop the definitive pertussis vaccine. FDA's efforts to assess the variety and extent of adverse reactions to pertussis vaccine are discussed elsewhere in this response.

Several laboratories, including those at CDB and NIAID in NIH, have been involved in studies that have resulted in the isolation, purification, and characterization of two vaccine candidates; lymphocytosis promoting toxin and filamentous hemagglutinin (Ref. 16). Several in vivo and in vitro models for research on the infectious process and its prevention have been established (Refs. 17, 18, and 19). A contract for basic studies on the biochemical and genetic characterization of *Bordetella pertussis* has been completed (Refs. 20 through 25).

The need for research on *Bordetella pertussis*, pertussis, and pertussis vaccine was emphasized in an *International Symposium on Pertussis* sponsored by FDA's former Bureau of Biologics, NIAID, CDC, the International Association of Biological Standardization, and The Fogarty International Center in 1978. The proceedings of the symposium have been published and widely distributed (Ref. 26).

The International Symposium on Bacterial Vaccines was covened at the National Institutes of Health in 1980. The conference was sponsored by NIH, FDA, Walter Reed Army Institute of Research, CDC, and the Department of Agriculture. Recent findings from research on bacterial vaccines, including pertussis vaccine, were reported. The proceedings of the meeting have been published (Ref. 27).

In February 1982, a workshop on "New Pertussis Vaccines—Laboratory and Clinical Evaluation" was held to discuss the technical, legal, logistical, and ethical problems associated with the clinical testing of the new acellular pertussis vaccines. The workshop was sponored by FDA, NIH, and CDC and was attended by scientists from 11 foreign countries and WHO.

In the **Federal Register** on June 1, 1984 (49 FR 22873), FDA announced an opportunity for the public to participate in collaborative laboratory tests on a proposed new lot of U.S. Standard Pertussis Vaccine and submit to FDA the results of the tests. FDA will consider any test data that are submitted concerning potency, stability, ampoule-to-ampoule variation, and toxicity during its final evaluation of the suitability of the proposed new lot. If its final evaluation is satisfactory, FDA intends to use the new lot of vaccine as the U.S. Standard Pertussis Vaccine, when the current lot of the standard vaccine is depleted. The biologics regulations (21 CFR 610.20) require that manufacturers must assure that each new lot of Pertussis Vaccine sold commercially is equivalent to the U.S. Standard Pertussis Vaccine.

22. The Panel recommended that the results of a WHO field trial in India to evaluate BCG vaccines be evaluated when the data become available, and that consideration be given to recommending that all BCG vaccines distributed in the United States be prepared from the same seed lot strain with demonstrated efficacy, if the data justify such an action.

The results of the WHO field trial in India have become available since the Panel's report was submitted (Refs. 28, 29, and 30). For the specific region of India in which the vaccine trial was conducted, the evidence indicates that BCG vaccine did not protect against bacillary pulmonary tuberculosis. The results should not be interpreted to mean that BCG vaccine would be ineffective for other populations of the world. Indeed, a prevalence of nontuberculous mycobacteria has been demonstrated in the trial region (Chinglepat, South India). Infection with such generally nonpathogenic mycobacteria is capable of conveying immunity and use of BCG vaccine may not have been able to increase this immunity significantly. The South India trial did not provide sufficient information on the effects of BCG vaccine in infants and young children. Continued followup should provide more information.

Because there is no conclusive evidence from the WHO BCG vaccine trial as to which strain is efficacious, it is not possible to implement the Panel's recommendation that all U.S. licensed BCG strains be prepared from the same seed lot strain with demonstrated efficacy.

23. The Panel recommended public support for development of an improved cholera vaccine, believing that such support is warranted because unsatisfactory sanitary conditions in many countries make is clear that control of the disease by sanitation alone cannot be realized in the foreseeable future.

FDA agrees with the recommendation. Other government agencies have been involved in programs to develop and to evaluate new types of vaccines and to study the pathogenesis of cholera. CDB has participated in selected aspects of these programs. Cholera is not an important disease in the U.S. at the present time, although a number of cases have been identified in the U.S. recently (Ref. 31). The major risk for cholera is to travelers to certain countries and to citizens of countries where the disease is endemic. Toxigenic

E. Coli disease is also an important cause of enteric disease in travelers. The recognition of the immunochemical simiarities and of the apparently identical mechanism of action of cholera toxin and the heat labile toxin of *E. coli* (Ref. 32) have resulted in increased research toward developing vaccines for these types of toxins. The Office of Biologics Research and Review will continue to monitor progress in these areas and will develop programs as necessary to evaluate these products.

24. The Panel recommended that the following plague vaccine immunization schedule should be considered: (a) a primary series of 3 intramuscular injections (1 mL, 0.2 mL, and 02 mL) 1 and 6 months apart, respectivly; (b) booster intramuscular inoculations of 0.2 mL at 12, 18, and 24 months; and (c) for persons achieving a titer of 1:128 after the third and fifth inoculation, further booster doses should be administered under the following circumstances: (i) When the passive hemagglutination titer falls below 1:32; (ii) empirically every 2 years when the patient cannot be tested serologically.

The agency agrees with the Panel's recommended immunization schedule for plague vaccine and notes that the current product labeling (since 1975) and the current ACIP recommendations (1982, Ref. 33) follow this schedule. The Panel had completed its review of plague vaccine before the revised package insert became available for its review. The Panel's recommendation and the current labeling are based on studies done by the U.S. Army with a plague vaccine manufactured exclusively for military use; however, the vaccine formulation for civilian use is now the same as that used the U.S. military and the labeling has been revised accordingly.

25. Regarding typhoid vaccine, the Panel recommended that (a) appropriate support should be given to studies aimed at clarifying the immune mechanism(s) in typhoid fever; (b) field or volunteer studies designed to test promising vaccines or their fractions for protection against typhoid fever should be supported; and (c) a search for laboratory tests of potency that correlate well with results of vaccination in humans should be conducted.

FDA agrees with the recommendations. However, ACIP has reported that "the incidence of typhoid fever has declined steadily in the U.S. in the last half century * * * The continuing downward trend is due largely to better sanitation and other control measures; vaccine is not deemed to have played a significant role * * * Routine typhoid vaccination is no longer recommended for persons in the U.S. * * *" (Ref. 34). Typhoid fever is decreasing in the U.S. civilian population, but the need is recognized for the ability to immunize selected personnel against enteric disease, including typhoid. In addition, typhoid fever remains a problem in other parts of the world. Although FDA itself is not prepared at this time to allocated significant resources to studies aimed at clarifying the immune mechanisms in typhoid, other government agencies are providing support for such studies. Field and volunteer studies are being supported by both government and private institutes. A new type of live oral vaccine has been field tested in Egypt (Ref. 35).

The agency will continue to review and evaluate laboratory procedures that may be suitable for correlating with the immune response of humans following vaccination. New methods for evaluating potency may be required for oral vaccines.

26. FDA proposes to amend § 610.21 (21 CFR 610.21) by requiring a minimum potency of not less than 250 units of tetanus antitoxin per container for Tetanus Immune Globulin (Human) (TIG).

The Panel noted that TIG is usually marketed in 250 unit amounts. Indeed, all currently licensed TIG is marketed with a labeled potency of 250 units per container. The specific antitoxin activity of the globulin is such that in the final product, 250 units has been contained in anywhere from approximately 0.6 to 4.0 mL of fluid, depending on the manufacturer's specifications, the starting potency of the purified globulin, and the type of container (vial or syringe) in which the product is to be marketed.

Under current § 601.21, the minimum potency of TIG must be not less than 50 units of tetanus antitoxin per milliliter (μ/mL). Because the volume of the final product has varied without any apparent effect on the performance of the product, FDA has determined that it is inappropriate to regulate the potency of TIG on a per volume (mL) basis. However, FDA notes that TIG currently is manufactured consistently at a concentration of 170 μ/mL or greater. FDA believes that TIG should continue to be manufactured at a comparable concentration, although not specifically required by regulation. The Panel found TIG to be effective based on the historical evidence of the clinical use of TIG for the prevention and treatment of tetanus. TIG has consistently been administered at doses of 250 units or larger. FDA believes that TIG should continue to be marketed at a potency no less than the potency of the minimum dose (250) units) which historically has been shown to be effective.

The 250 units per container would represent the minimum potency of TIG permitted throughout the dating period of the product. Under § 610.53(a) (21 CFR 610.53(a)), TIG is prescribed a dating period of 3 years, provided three is an initial 10 percent excess of potency. Accordingly, a potency of 275 units per container (250 units plus 10 percent excess) would be required at the date of manufacture. FDA advises that in this discussion and the proposed regulation "per container" is interpreted to be that amount of the contents of the container that is deliverable to the patient in normal use. All current manufacturers of licensed TIG already conform to the proposed requirement by marketing the product in 250 unit amounts, plus an excess of at least 10 percent. Thus, FDA believes the proposed amendment would make the regulations consistent with current practices.

D. Response to General Research Recommendations

27. Throughout its Final Report, the Panel identified many areas in which there should be further investigation, beyond that immediately required of a manufacturer for a safe, effective, and properly labeled licensed product. Included were recommendations to monitor the population for its immune status against several bacterial diseases, suggestions for improving existing bacterial products and developing new products, and recommendations for developing laboratory tests and animal models correlated with the clinical potency of certain bacterial products.

FDA agrees with the recommendations. There are many areas surrounding the manufacture, testing, and use of bacterial vaccines, toxoids, and other bacterial products that require further investigation. FDA, through its Office of Biological Research and Review, continues to participate in these efforts. In this response, the agency has responded to several specific recommendations to initiate further investigations to help assure the safety, purity, and potency of currently licensed products. FDA will continue to consider the Panel's findings and recommendations when initiating or supporting investigative studies.

The agency notes that some of the investigations recommended by the Panel, such as monitoring the immune status of the population, are primarily

the responsibility of other agencies. To aid in the development of new or improved vaccines, FDA continues to participate in basic research to gain a better understanding of disease mechanisms and the physiology of the causative organisms. FDA also supports vaccine development by reviewing study protocols and data and by aiding in the development of laboratory tests suitable for assuring the safety, purity, and potency of the product. Many of the organizations involved in the study of bacterial disease and the development of bacterial products already are aware of the Panel's recommendations through their attendance at Panel deliberations. Through the publication and broad dissemination of the Panel's Report, FDA is encouraging the cooperation of public and private organizations to achieve the research objectives recommended by the Panel.

In several cases, the Panel recommended the development of a new biological product for the prevention or cure of a rare disease. FDA believes that these products may not have been developed in the past because of insufficient commercial incentive to justify the considerable expense for manufacturers involved in the development and clinical testing of new drug products. Drugs intended for rare disease are commonly called "orphan drugs."

The Orphan Drug Act (Pub. L. 97–414) became law on January 4, 1983. The Orphan Drug Act establishes a number of incentives to facilitate the development and marketing of drugs, including biological drugs, for rare diseases or conditions. FDA has created an Office of Orphan Products Development to coordinate FDA's efforts to assist manufacturers in the development of orphan drugs. FDA has announced in the **Federal Register** the availability of interim procedures to implement the Orphan Drug Act (48 FR 40784; September 9, 1983).

In the following paragraphs FDA is summarizing its response to those Panel recommendations that require further investigations for developing or improving biological products.

a. *Animal models and laboratory tests for demonstrating vaccine efficacy.* The Panel recommended that the public support the development of animal models that accurately predict vaccine responses in humans. The Panel specifically mentioned animal models for diphtheria toxoid, tetanus toxoid, BCG vaccine, plague vaccine, and pertussis vaccine as needing further development. The Panel also found that increased emphasis is needed on the development of laboratory tests and procedures that would reflect vaccine efficacy with sufficient accuracy so as to minimize the need for field trials.

FDA agrees that there are needs for assay systems that predict primary immunogenicity in humans, especially in view of the increasing difficulty in finding suitable populations for conducting clinical studies for many types of vaccines.

The development of animal models and laboratory procedures that accurately reflect vaccine responses and effectiveness in humans require that vaccines of varying potency or strength be administered to humans so that accurate correlations can later be made with the animal and laboratory models being developed. DHHS is actively involved in fundamental programs requisite to such studies, particularly as previously discussed for toxoids and pertussis vaccine. The agency is involved in the operation of primate breeding colonies to assure a sufficient number of primates for research, including vaccine testing. Monkeys have been used by the Office of Biologics Research and Review for studies of toxoid potency. Laboratory techniques are modified to meet changing technical advances applicable to all products.

The agency is currently funding work directed, in part, toward the development of a radioimmune assay method for the sensitive evaluation of serologic responses of animals and man to plague vaccine, which may eliminate the need for expensive, time-consuming, and less precise animal challenge experiments.

The following factors make it unlikely that the development and evaluation of BCG vaccines in animal model systems will have high priority at this time: (1) the low incidence of tuberculosis in this country; (2) the availability of effective drugs for treating the disease; (3) the need for unassailable evidence for the clinical effectiveness of a specific vaccine in protecting humans against the disease; and (4) limited Federal resources.

b. *Unmet needs for vaccines.* The Panel found research is needed to fulfill unmet needs in protection against bacterial diseases such as streptococcal, staphylococcal, gonococcal, *Haemophilus influenzae,* and pseudomonas infections.

The Office of Biologics Research and Reviews investigating the immune response to selected encapsulated bacteria and the development of methods of providing safe and effective vaccines to prevent diseases caused by such bacteria. The purified capsular polysaccharides of these organisms have been shown to be inadequate immunogens because most of them elicit a poor immune response in infants less than 2 years of age, the age at which diseases caused by these organisms are most prevalent. Further, reinjection of these polysaccharides is unsuccessful in providing protection as they exert no booster effect. A field trial of *Haemophilus influenzae* type b polysaccharide vaccine, conducted in Mecklenberg County, was supported by FDA. The Office of Biologics Research and Review has investigated covalent binding of bacterial polysaccharides, especially *H. influenzae* type b, Pneumococcus type 6, and *E. coli* K13 and K1 to immunogenic and T-dependent carrier proteins.

The Office of Biologics Research and Review has studied *N. meningitidis* serotype proteins and lipopolysaccharides as serological and epidemiological tools for characterizing *N. meningitidis* strains. The Office of Biologicals Research and Review is investigating as a vaccine candidate serotype 2 protein (found in over 50 percent of the group B strains and in group C strains) in combination with the group B capsular polysaccharide.

Collaborative studies were initiated to defined the structural character of staphylococcal capsules. To date, 10 capsular types have been serologically defined, 2 of which were found to be associated with human disease. The studies were performed to purify and analyze the structure of these polysaccharides, which may provide protection staphlococcal antigens (see Ref. 41 below).

c. *Bacterial toxins.* The Panel recommended support for research on the mechanism of action of bacterial toxins, specifically botulism and histotoxic clostridia toxins.

FDA recognizes the need for studies on the mechanism of action of bacterial toxins. FDA has supported work on other aspects of botulism toxins and is actively engaged in research on the mechanisms of actions of several other bacterial toxins, including tetanus toxin. This latter work may prove relevant to botulism toxin because both toxins appear to inhibit neurotransmitter relase. Other government agencies are supporting work on botulism (see Ref. 39 below).

At this time, FDA does not intend to undertake studies of the histotoxic clostridia. The acceptable mode of therapy of gas gangrene is surgery, antibiotics, and other supportive therapy; the use of passive immunization with the polyvalent gas gangrene antitoxin has been, at most, adjunctive. As noted in the Panel's

review, there is no evidence that the antitoxin product available in this country is effective and there is general agreement that such products are not effective for prophylactic use. FDA is aware of the emergence of clostridia as pathogens in enteric diseases. FDA will reevaluate the need for increased effort in this area as new data become available. The agency is supplying antitoxins to investigators for studies in this area.

d. *Immune globulins.* In a number of instances, the Panel recommended support of research and testing for the improvement of currently licensed immune globulin products or the development of new products conferring passive immunity. Specifically the Panel recommended that:

(1) The development of botulism and diphtheria immune globulin preparation of human origin be considered;

(2) Studies be supported to provide further information in judging the prophylactic and therapeutic value of Tetanus Immune Globulin (Human) (TIG) and to establish the availability, safety, potency, and stability of TIG for intravenous use;

(3) The accumulating data on intrathecal therapy be reviewed and followed to determine its possible application in treating human tetanus with TIG;

(4) The protective antibodies in the currently available Pertussis Immune Globulin (Human) be identified and characterized and that other immunoglobulin preparations be studied to determine their efficacy in conferring passive immunity to pertussis; and

(5) Further informtion be obtained regarding the possibility or reducing the reactivity of animal serum used in tetanus and diphtheria antitoxins.

FDA agrees with these recommendations. On October 31, 1979, in conjunction with the National Heart, Lung, and Blood Institute, FDA held a public workshop to discuss the characteristics and current and potential development and use of immunoglobulins. Some of the topics discussed at the workshop were: The European experience with the use of I.V. preparations, the current and potential uses of I.M. and I.V. preparations, and the causes and prevention of clinical reactions to these products. The information provided at this workshop will aid interested manufactures and FDA in developing and assessing new immunoglobulins, including those for I.V. administation. In late 1981, Immune Globulin Intravenous manufactured by Cutter Laboratories, Inc., was licensed for sale in the United States.

Researchers have shown it is possible to prepare a diphtheria immune globulin (Ref. 36 and 37). The effectiveness of this type of preparation for either prophylaxis or therapy has not been demonstrated, but FDA is encouraging the development of such a product.

Development of a botulism immune globulin is in progress (Ref. 38 and 39). The agency supports further efforts to develop such a product.

FDA agrees with the Panel's observations that more information on the value of TIG in prophylaxis and therapy is needed. The Panel and FDA have both observed, however, that it would be difficult for ethical and epidemiological reasons to do controlled clinical trials of this product in te United States. The agency discusses elsewhere in this response the problem of developing animal models that accurately predict human response to biologicals, including TIG. The agency is aware of the growing body of conflicting data regarding the intrathecal administration of TIG and will continue to monitor information regarding this use.

The Office of Biologics Research and Review has an active research program directed at identifying and purifying the bacterial components necessary for prevention of pertussis (Ref. 16, 17, and 18). Animal models to study the infection and its prevention by active and passive immunization have been developed (Ref. 19). As indicated previously, FDA's former Bureau of Biologics has sponsored several symposia and/or workshops regarding pertussis. These meetings have provided forums for discussion of this disease and its prevention and treatment. FDA will continue to support the development of new or improved products for the prevention and treatment of pertussis.

FDA believes that priority should be given to developing suitable homologous antitoxins unless experimental data can be provided to show that antitoxins developed in animals have superior immunologic of therapeutic properties compared to that of human immune globulin and are potentially less reactive than current equine antitoxins. However, the agency is interested in manufacturing procedures which may reduce the reactivity of animal serum products because animal sera are more available throughout the world. Methods to immunopurify equine antitoxin have been reported (Ref. 40) and may have expanded application. The ability to produce monoclonal antibodies utilizing cell cluture techniques can be expected to provide new types of antitoxins in the future. The Office of Biologics Research and Review is engaged in research in this area and is willing to evaluate new products generated by this important technology.

References

1. Cody, C.L., et al., "Nature and Rates of Adverse Reactions Associated with DTP and DT Immunizations in Infants and Children," *Pediatrics*, 68:650–660, 1981.

2. Barkin, R.M. and M.E. Pichichero, "Diphtheria-Pertussis-Tetanus Vaccine: Reactogenicity of Commercial Products," *Pediatrics*, 63:256–260, 1979.

3. Hopkins, R.S., "Reactions to DTP Vaccine, by Lot and Manufacturer; Results of a Survey in Montana," *in* "International Symposium on Pertussis," edited by C.R. Manclark and J.C. Hill, Department of Health, Education, and Welfare Publication No. (NIH) 79–1830, 1979.

4. E. N. Brandt, Jr., "Remarks to Conferees," at the Sixteenth Immunization Conference, Centers for Disease Control, Atlanta, May 19, 1981.

5. Jaekel, J. F., et al., "A Study of Trends in Upper Arm Soft Tissue Sarcomas in the State of Connecticut Following the Introduction of Alum-Adsorbed Allergenic Extract," *Annals of Allergy*, 40:28–31, 1978.

6. "News From the National Institute of Allergy and Infectious Disease. Summary of an International Symposium on Potentiation of the Immune Response to Vaccines," *The Journal of Infectious Diseases*, 141:103–112, 1980.

7. World Health Organization Expert Committee on Biological Standardization Technical Report Series 638: "Requirements for Diphtheria Toxoids, Pertussis Vaccine, and Tetanus Toxoid, and Combined Vaccines," World Health Organization, Geneva, Switzerland, 1981.

8. "Recommendations of the Immunization Practices Advisory Committee (ACIP), Diphtheria, Tetanus, and Pertussis: Guidelines for Vaccines Prophylaxis and Other Preventive Measures," *Morbidity and Mortality Weekly Report*, 30:392–406, 1981.

9. Van Ramshorst, J. D. and T. K. Sundaresan, "Collaborative Assay of a Proposed International Standard for Tetanus Toxoid (Adsorbed)," *Bulletin of the World Health Organization*, 46:53–66, 1972.

10. Van Ramshorst, J. D., et al., "International Collaborative Studies on Potency Assays of Diphtheria and Tetanus Toxoids," *Bulletin of the World Health Organization*, 46:263–276, 1972.

11. Pittman, et al., "Immunization Against Neonatal Tetanus in New Guinea. 5. Laboratory Assayed Potency of Tetanus Toxoids and Relationship to Human Antitoxin Response," *Bulletin of the World Health Organization*, 43:469–478, 1970.

(12) Hardegree, C. M., et al., "Titration of Tetanus Toxoids in International Units: Relationship to Antitoxin Responses of Rhesus Monkeys," *in* "Sixth International Conference on Tetanus," Collection Foundation Merieux (publisher), Lyon, France, December 3 to 5, 1981.

(13) Edsall, G., et. al., "Host Factors in the Response to Immunization," *Progress in Drug Research*, 19:263–273, 1975.

(14) Manclark, C. R. and B. D. Mead, "Serological Response to *Bordetella pertussis," in* "Manual of Clinical Immunology," 2d Ed., Edited by N. R. Rose and H. Friedman, the Williams and Wilkins Co., Baltimore, pp. 496–499, 1980.

(15) "Pertussis (Whooping Cough)," *in* "Report of the Committee on Infectious Diseases (the Red Book)," 19th Ed., Jerome O'Klein, editor, American Academy of Pediatrics, Evanston, IL, pp. 198–202, 1982.

(16) Cowell, J. L., et al., "Separation, Purification, and Properties of the Filamentous Hemagglutinin and the Leukocytosis Promoting Factor-Hemagglutinin from *Bordetella pertussis," in* "Seminars in Infectious Disease, Vol. IV, Bacterial Vaccines," edited by J. B. Robbins, J. C. Hill, and G. Sadoff, Brian C. Decker Division, Thieme-Stratton Inc., New York, pp. 371–379, 1982.

(17) Sato, Y., et al., "Role of Antibody to the Filamentous Hemagglutinin and to the Leukocytosis Promoting Factor-Hemagglutinin in Immunity to Pertussis," *in* "Seminars in Infectious Disease, Vol. IV, Bacterial Vaccines," edited by J. B. Robins, J. C. Hill, and G. Sadoff, Brian C. Decker Division, Thieme-Stratton Inc., New York, pp. 380–385, 1982.

(18) Sato, Y., et al., "Role of Antibody to the Leukocytosis-Promoting Factor and to the Filamantous Hemmagglutinin in Immunity to Pertussis," *Infection and Immunity,* 31:1223–1231, 1981.

(19) Sato, Y., et al., "Aerosol Infection of Mice with *Bordetella pertussis," Infection and Immunity,* 29:261–266, 1980.

(20) Kloos, W. E., et al., "DNA-DNA Hybridization, Plasmids, and Genetic Exchange in the Genus *Bordetella," in* "International Symposium on Pertussis," edited by C. R. Manclark and J. C. Hill, DHEW (NIH) 79–1830, U.S. Government Printing Office, Washington, DC pp. 70–80, 1979.

(21) Dobrogosz, W. J., et al., "Physiology of *Bordetella pertussis," in* "International Symposium on Pertussis," edited by C. R. Manclark and J. C. Hill, DHEW (NIH) 79–1830, U.S. Government Printing Office, Washington, DC, pp. 86–93, 1979.

(22) Ezzell, J. W., et al., "Phase-Shift Markers in *Bordetella:* Alterations in Envelope Proteins," *The Journal of Infectious Diseases,* 143:562–569, 1981.

(23) Hall, G. W., et al., "Repression of Adenyulate Cyclase in the Genus *Bordetella," Microbios, 33:45–52, 1982.*

(24) Ezzel, J. W., et al., "Phase shift Markers in the Genus *Bordetella:* Loss of Cyochrome d-629 in Phase IV Variants," *Microbios,* 31:171–182, 1981.

(25) Kloos, W. E., et al., "Deoxyribonucleotide Sequence Relationships Among *Bordetella* Species," *International Journal of Systemic Bacteriology,* 31:173–176, 1981.

(26) Manclark, C. R. and J. W. Hill (eds.), "International Symposium on Pertussis," Publication No. DHEW (NIH) 79–1830, U.S. Government Printing Office, Washington, DC, 387 pp. 1979.

(27) "Seminars in Infectious Disease, Vol. IV, Bacterial Vaccines," edited by J. B. Robbins, J.C. Hill, and G. Sandoff, Brian C. Decker Division, Thieme-Stratton, Inc., New York, 461 pp., 1982.

(28) World Health Organization, Technical Report Series 651, "Vaccination Against Tuberculosis; Report of an ICMR/WHO Scientific Group," World Health Organization, Geneva, Switzerland, 1980.

(29) World Health Organization, Technical Report Series 652, "BCG Vaccination Policies; Report of a WHO Study Group," World Health Organization, Geneva, Switzerland, 1980.

(30) "BCG Vaccination After the Madras Study," *The Lancet,* February 7, 1981.

(31) "Cholera 1981," *Morbidity and Mortality Weekly Report,* 31:481–482, 1982.

(32) Moss, J. and M. Vaugh, "Mechanism of Action of Cholergan and *E. coli* Heat-Labile Entrotoxin: Activation of Adenylate Cyclase by ADP-Ribosylation," *Molecular and Cellular Biochemistry,* 37:75–90, 1981.

(33) "Plague Vaccine, Recommendations of the Immunization Practices Advisory Committee (ACIP)," *Morbidity and Mortality Weekly Report,* 31:301–304, 1982.

(34) "Recommendation of the Immunization Practices Advisory Committee (ACIP); Typhoid Vaccine." *Morbidity and Mortality Weekly Report,* 27:231–232, 1978.

(35) Wahdan, M. H., et al. "A Controlled Field Trial of Live *Salmonella typhi* Strain Ty 21a Oral Vaccine Against Typhoid: Three-year Results," *The Journal of Infectious Diseases,* 145:292–295, 1982.

(36) Sgouris, J.T., et al., "Studies on Diphtheria Immune Globulin Prepared from Outdated Human Blood," *Vox Sanguines,* 16:491–495, 1969.

(37) Hartman, L.J., "Bioavailability Study of Diphtheria Immunoglobulin (human)," *Pathology,* 11:385–387, 1979.

(38) Metzger, J.F., and G.E. Lewis, "Human-Derived Immune Globulins for the Treatment of Botulism," *Review of Infectious Disease,* 1:689–690, 1979.

(39) Lewis, G.E., "Approaches to the Prophylaxis, Immunotherapy, and Chemotherapy of Botulism," *in* "Biomedical Aspects of Botulism," Academic Press, Inc., New York, 1981.

(40) Tardy, M., et al., "A New Preparation of Equine Tetanus Antibodies Purified by Pepsin Hydrolysis and Immunoadsorbtion," *in* "Sixth International Conference on Tetanus," Collection Foundation Merieux (publisher), Lyon, France, December 3 to 5, 1981.

(41) Fournier, J.M., W.F. Vann, and W.W. Karakawa "Purification and Characterization of Staphylococcus aureus Type 8 capsular Polysaccharide," *Infection and Immunity,* 45: 87–93, 1984.

The agency has determined pursuant to 21 CFR 25.24(d) (2) and (10) (proposed December 11, 1979; 44 FR 71742) that this action is of a type that does not individually or cumulatively have a significant impact on the human environment. Therefore, neither an environmental assessment nor an environmental impact statement is required.

FDA has examined the regulatory impact and regulatory flexibility implications of the proposed regulation in accordance with Executive Order 12291 and the Regulatory Flexibility Act. The agency concludes that 18 manufacturers of bacterial vaccines and toxoids and related products will be affected by these requirements, of whom approximately 3 are small. No additional costs are expected to be incurred as a result of this rulemaking. The anticipated costs are insufficient to warrant designation of this proposal as a major rule under any of the criteria specified under section 1(b) of Executive Order 12291 or to require a regulatory flexibility analysis. Accordingly, under section 605(b) of the Regulatory Flexibility Act, the Commissioner of Food and Drugs certifies that this rulemaking, if promulgated, will not have a significant economic impact on a substantial number of small entities. A copy of the threshold assessment supporting this determination is on file with the Docket Management Branch, FDA (address above).

List of Subjects in 21 CFR Part 610

Biologics, Labeling.

Therefore, under the Federal Food, Drug, and Cosmetic Act, the Public Health Service Act, and the Administrative Procedure Act and under 21 CFR 5.11, it is proposed that Part 610 be amended as follows:

PART 610—GENERAL BIOLOGICAL PRODUCTS STANDARDS

1. The authority citation for 21 CFR Part 610 continues to read as follows:

Authority: Sec. 215, 58 Stat. 690 as amended, 42 U.S.C. 216, sec. 351, 58 Stat. 702 as amended, 42 U.S.C. 262; 21 CFR 5.10 and 5.11.

2. In § 610.21 by revising the item "Tetanus Immune Globulin (Human)" under the heading "ANTIBODIES" to read as follows:

§ 610.21 Limits of potency.

* * * * *

Antibodies

* * * * *

Tetanus Immune Globulin (Human), 250 units of tetanus antitoxin per container.

* * * * *

Interested persons may, on or before March 13, 1986, submit to the Dockets Management Branch (HFA–305), Food and Drug Administration, Rm. 4–62, 5600 Fishers Lane, Rockville, MD 20857, written comments regarding this proposal. Two copies of any comments are to be submitted, except that individuals may submit one copy. Comments are to be identified with the docket number found in brackets in the

heading of this document. Received comments may be seen in the office above between 9 a.m. and 4 p.m., Monday through Friday.

Dated: October 11, 1985.

Frank E. Young,

Commissioner of Food and Drugs.

Margaret M. Heckler,

Secretary of Health and Human Services.

[FR Doc. 29206 Filed 12–12–85; 8:45 am]

BILLING CODE 4160–01–M